

REMARKS

Applicants wish to thank Examiner Lao and supervisory Examiner Witherspoon for the helpful discussion on December 3, 2007. During the discussion, the Examiners indicated that the Examples in the specification may be sufficient to overcome any *prima facie* case, however, they wanted to further review the case. The following is intended to expand on the discussion with the Examiners.

Claims 1-24 are active in the present application. Independent Claim 1 is amended as supported by Claims 2-4 and the specification as originally filed. Claims 23 and 24 are new claims. Support for new Claim 23 is found on page 3, line 16. Claim 24 is supported by Claims 1, 3, 7 and 21 as originally filed.

No new matter is added.

The present application describes a process for reacting a piperidone with gaseous hydrogen chloride to ketalize the piperidone. Applicants disclose on page 1 of the present specification that although the formation of ketals from a piperidone such as triacetonamine has been reported before, the prior art processes are carried out by using a reactant in its aqueous form or by using an organic acid such as p-toluenesulfonic acid.

**Certain disadvantages inhere to processes carried out by using aqueous inorganic acids or organic acids.** For example, the amine portion of the piperidone may convert to a salt form thus absorbing substantial amounts of the acid catalyst. When this happens, each mole of the reactant absorbs one mole of the catalyst and thus a substantially greater than a catalytic amount of the acid is required.

It is an object of the invention to provide a process for preparing open-chain or cyclic ketals, in particular of triacetonamine, which does not have the abovementioned disadvantages and which in particular starts from simple starting compounds, does not require any additional synthesis and isolation steps and can be carried out without any problems on an industrial scale. See page 2, lines 9-13 of the specification.

It has been found that, **surprisingly**, triacetonamine can be reacted with hydroxyl derivatives having one or more hydroxyl groups, in particular mono- or polyhydric alcohols, and **with gaseous hydrogen chloride without any undesired side reactions**, for example chlorination of the hydroxyl group, taking place to a significant extent. See page 2, lines 15-18 of the specification.

The invention therefore provides, in **amended Claim 1**, a process for ketalizing triacetonamine, which comprises:

reacting triacetonamine and a hydroxyl derivative having one or more hydroxyl groups **with gaseous hydrogen chloride in a non-polar solvent** to yield the open-chain or cyclic triacetonamine ketal.

In **Claims 3 and 4, specific solvents** are claimed.

In **Claim 21** it is claimed that the reacting is carried out with **gaseous hydrogen chloride as the only catalyst**.

In **Claim 23** it is claimed that **no further acid catalyst** is used.

**New Claim 24** provides a process for ketalizing triacetonamine, which comprises:

reacting triacetonamine and a hydroxyl derivative having one or more hydroxyl groups with gaseous hydrogen chloride in a solvent to yield the open-chain or cyclic triacetonamine ketal,

wherein the solvent is an acyclic hydrocarbon, a cyclic hydrocarbon, or an aromatic hydrocarbon,

wherein the reacting forms water which is removed from the reaction mixture,  
and

wherein the reacting is carried out with gaseous hydrogen chloride as the only  
catalyst.

The advantages of carrying out the ketalization of piperidone as presently claimed are described in the present specification on page 5, line 25 through page 6, line 23. Such advantages include a reduced amount of hydrogen chloride usage, reduced waste, improved yield of the desired product, reduced by-product formation, reduced reaction time, and simplification of purification:

“The ketalization of triacetonamine with gaseous hydrogen chlorides has significant advantages:

Compared to a reaction with concentrated hydrochloric acid, the reaction of triacetonamine with the hydroxyl derivative and hydrogen chloride gas can be carried out quantitatively without any problems. For instance, the reactions of triacetonamine with ethylene glycol and concentrated aqueous hydrochloric acid which have been carried out as comparative experiments showed that as soon as excess water (and therefore excess hydrogen chloride) had been removed, the reaction mixture has attained a pH of only 4-5 and the conversion remained at approx. 80-85%. Even when p-toluenesulfonic acid was added and water was repeatedly removed, complete conversion of triacetonamine could not be achieved.

**Triacetonamine is ketalized substantially faster using hydrogen chloride gas as the acid compared to reaction using concentrated aqueous hydrochloric acid, since the excess amount of water does not first have to be removed again from the reaction mixture.** It is therefore possible by the process according to the invention to achieve a substantially higher space-time yield in comparison to the use of concentrated aqueous hydrochloric acid.

Comparative experiments have shown that when sulfuric or phosphoric acid is used as the catalyst, considerable amounts of by-products are formed, which can presumably be attributed to a decomposition of triacetonamine. This by-product formation is avoided by the process of the present invention.

The waste occurring in the process according to the invention after neutralization with a base is only the corresponding chloride salt (for example sodium chloride) which can be disposed of significantly better (or less expensively) than other salts, for example sodium sulfate, sodium phosphate or the corresponding sulfonic acid salt.

Hydrogen chloride gas is inexpensive, can be metered accurately and is often available via a gas line on the industrial scale. As a consequence, hydrogen chloride gas can be easily handled and incurs virtually no storage costs.”

**Emphasis added.**

In addition, the specification states at page 3, line 17 to page 4, line 6:

“When carrying out the process according to the invention, it is found that, **completely unexpectedly, as early as during the introduction of the gaseous hydrogen chloride and therefore before the complete saturation of the secondary amine function, triacetonamine or the triacetonamine hydrochloride formed in situ are converted to the particular triacetonamine ketal.** Although the reaction mixture therefore only has the acidic pH required for a ketalization toward the end of the hydrogen chloride uptake, the triacetonamine conversion at this time for most triacetonamine ketals is **surprisingly at 80-95%.** It is also possible to use the gaseous hydrogen chloride in a superstoichiometric amount. If desired, the water of the reaction formed in the ketalization can also be subsequently removed from the system, preferably by azeotropic distillation, and the conversion completed in this way.

After neutralization of the reaction mixture and appropriate workup (for example by distillation or filtration and washing), the particular triacetonamine ketals are obtained in high yield and in high purity.”

**Emphasis added.**

The **Examples of the present specification** show that high product yields are achievable when gaseous HCl is used in combination with non-polar solvents. **Examples 1-4** of the present specification provide yields of the desired product which are 76% and greater.

On the other hand, in **Comparative Examples 1-3**, large amounts of by-product are produced. In Comparative Example 1, “large amounts of a water-insoluble solid precipitated

out and collected as sticky deposits on the flask and stirrer.” In Comparative Example 2, “there was less than 10% of the desired product according to the gas chromatogram. Instead, a plurality of secondary components had formed which were not investigated further.” In Comparative Example 2, “the conversion remained at approx. 80-85%. After adding p-toluenesulfonic acid as a catalyst and removing water again, the conversion could be increased slightly, although even after adding and removing water three times, quantitative TAA conversion was not achieved.”

Naohiro and Buzzard fail to disclose or suggest a process as claimed in which triacetonamine and a hydroxyl derivative having one or more hydroxyl groups are reacted with gaseous hydrogen chloride in a non-polar solvent to yield the open-chain or cyclic triacetonamine ketal.

The drawbacks of using an aqueous-type acid which may form a salt of a piperidone are well-demonstrated by Naohiro. Control 1-1 in column 4 of Naohiro describes the reaction of a hydrogen chloride form of triacetonamine. In Control 1-1, the hydrochloride form of triacetonamine (e.g., the salt form) is reacted in the presence of the organic acid p-toluenesulfonic acid to form a ketal. The product yield obtained for the Control Examples and the Inventive Examples of Naohiro are described in Table 1 in columns 5-6. As is readily evident from Table 1 of Naohiro, the reaction of the salt form of the triacetonamine provides a very low product yield (i.e., no greater than 47%).

Examples 1-1 through 1-8 of Naohiro show the effect of using a polar solvent when p-toluenesulfonic acid is used as a catalyst. These Examples show that yields of 84-94% are achievable when a polar solvent is used in combination with p-toluenesulfonic acid. Present Claim 3 requires the use of a solvent such as an acyclic hydrocarbon, a cyclic hydrocarbon, or an aromatic hydrocarbon that is different from the polar solvents of Naohiro.

Applicants submit that the Control Examples of Naohiro provide evidence that carrying out a ketalization process in the presence of an aqueous acid so that a salt form of the triacetonamine is formed as an intermediate, provides a lower purity product in lower yield.

Moreover, the examples of Naohiro do not provide any indication that the form of the triacetonamine may have an effect on the reaction. In fact, Naohiro's Table 1, at best, shows only that the choice of solvent may effect the reaction. Naohiro does not recognize that the form of the triacetonamine (e.g., salt form or base form) may have an effect.

The Office asserts that the presently claimed invention is obvious over Naohiro in view of Buzzard (WO 02/22593). The Office appears to be aware that present independent Claim 1 requires that the reacting (i.e., the reaction of triacetonamine with a hydroxyl derivative) is carried out in the presence of gaseous hydrogen chloride. The Office concedes that Naohiro does not disclose this aspect of the presently claimed invention (see the first full paragraph on page 3 of the January 8, 2007 Office Action). To remedy this deficiency, the Office relies upon Buzzard as evidence that it would be obvious to carry out a reaction using gaseous HCl.

At the outset, Applicants point out that the reactions of Naohiro and Buzzard are substantially different. Naohiro discloses the reaction of a piperidone with an alkanediol compound (see columns 7 and 8 of Naohiro) whereas Buzzard discloses the conversion of pentose or pentosan to furfural. Applicants submit that the reactions of Buzzard and Naohiro are substantially different. Naohiro discloses a reaction that is carried out on a six-membered heterocyclic ring whereas Buzzard discloses a reaction carried out on a five-membered carbon ring. Structures of triacetonamine and furfural obtained from www.sigmaaldrich.com were previously submitted.

It appears that the Office did not consider this difference between the reactants of Naohiro and Buzzard and provided no basis for asserting that the reactivity of a five-membered carbon ring would be applicable to the reactivity of a six-membered heterocyclic ring.

The six-membered heterocyclic ring of Naohiro includes an N atom. The N atom may be substituted with a R<sub>4</sub> group which may be a hydrogen atom or an alkyl group (see column 7, line 55). Applicants submit that when reacted with gaseous HCl such an N group-containing moiety would react in a substantially different manner than the five-membered carbon ring of Buzzard. For example, an amine group such as the amine group of the piperidone of Naohiro forms an HCl salt when exposed to or reacted with HCl. A salt form of the prior art starting material may have substantially different reactivity in comparison to the Naohiro starting material. A change to the salt form may provide a compound that is substantially different than the six-membered N atom group-containing starting material of the present claims.

Applicants submit that the Office provided no rational basis for combining the above-cited prior art. Because the reactants of Naohiro and Buzzard are so different and because the reactant of Naohiro would be expected to undergo different types of reactivity the combination of the prior art references is not proper. For at least this reason the rejection should be withdrawn and the claims should be allowed.

Not only are the starting materials and products of Naohiro and Buzzard different, the conditions under which the reactions carried out are also substantially different. Naohiro discloses that the reaction of the prior art six-membered heterocyclic ring is carried out “in the presence of a polar solvent” (column 3, lines 12-13 of Naohiro). In contrast, the reaction of Buzzard is carried out by heating the prior art five-membered hydrocarbon ring in the solid phase in the presence of a gaseous acid catalyst (see page 2, lines 12-14 of Buzzard). Further,

the pentose and pentosan of Buzzard are solid materials whereas the triacetonamine of the present claims is a liquid.

Applicants thus submit that the prior art relied upon by the Office is not properly combinable at least because (i) the starting reactants and finished products Naohiro and Buzzard are substantially different, and because (ii) the conditions of the Buzzard and Naohiro reactions are substantially different.

For the reasons discussed above, in view of the disparate starting materials, reactant conditions and final products. Applicants submit that those of ordinary skill in the art would have no basis for turning to use the disclosure of Buzzard as inspiration to modify the reaction of Naohiro. Applicants thus submit that the rejection is not supportable and should be withdrawn.

With regard to present **dependent Claim 3** which requires that the reaction is carried out in a solvent selected from the group that includes an acyclic hydrocarbon, a cyclic hydrogen carbon and an aromatic hydrocarbon, Applicants submit that the aforementioned subject matter is further patentable in view of the fact that Naohiro requires that the prior art reacting is carried out “in the presence of a polar solvent selected from the group consisting of alcohols having 1 to 13 carbon atoms and 1 alcoholic hydroxyl group, and amides of carboxylic acids having 1 to 4 carbon atoms” (see column 8, lines 34-38 of Naohiro).

Applicants also draw the Office’s attention to **dependent Claim 4** where the solvent is heptane, cyclohexane, ethylcyclohexane, toluene or xylene. Applicants submit that the subject matter of Claims 3 and 4 is further patentable over the combination of Buzzard and Naohiro in view of the fact that (i) Naohiro requires the presence of a polar solvent that has a hydroxyl or acidic group and (ii) Buzzard discloses a reaction that is carried out by contacting a reactant in the solid state with a second, gaseous material. Applicants therefore submit that

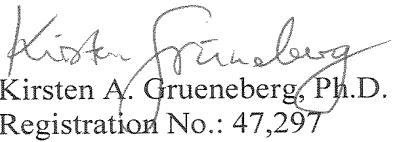
the rejection of Claims 3 and 4 in view of Naohiro and Buzzard is not supportable and should be withdrawn.

In view of the above, the rejections of record should be withdrawn.

For the reasons discussed in detail above, Applicants submit that all now-pending claims are in condition for allowance and request the mailing of a Notice of Allowance acknowledging the patentability of the present claims over the prior art relied upon by the Office.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, P.C.  
Norman F. Oblon

  
Kirsten A. Grueneberg, Ph.D.  
Registration No.: 47,297